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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,370	01/23/2001	Jeffrey Browning	A054 US	2716

7590 05/25/2004

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,370	BROWNING ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10,11,16,18,19,26-29 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10,11,16,18,19,26-29 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Browning *et al*
Priority Date: 17 December 1998

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/20/2004 has been entered.

2. Claims 1-7,9,12-15,17,20-25, and 30-36 are canceled without prejudice or disclaimer, claims 37-39 are newly added.

3. Claims 8,10-11,16,18-19,26-29, and 37-39 are therefore pending and examined on the merits.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Maintained - 35 USC § 102

5. The rejection of claims 8, 10, and now claims 26-28, and 39 under 35 USC 102(b) as being anticipated by Crowe *et al* is maintained for the reasons of record. Applicant further argues that the reference does not provide a composition that comprises at least 70% biologically active receptor-Ig fusion protein, nor does the

reference teach the construction of the composition at temperature conditions around 27-35 degrees C. Applicant also argues that the fusion product claimed is made in a different expression system. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The Crowe-Science reference provides disclosure of a receptor-Ig fusion protein wherein the receptor is a member of the TNF family of receptors (aka $TNFR_{60}$:FC). The claims are drawn to the product *per se* and as a result, the method by which the product is made is not considered a patentable distinction. MPEP 2113 states *"The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).* It is further stated that *"[T]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product." See, e.g., In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).* In the instant case, the product appears to be the same, with the only distinguishing difference allegedly being the activity of the fusion proteins and the culture system by which the fusion protein is made. This distinction does not address structural differences in the fusion protein, because the product claimed and that taught by Crowe *et al* appear to be identical. The limitations only recite the amount of "active"

protein but does not address or limit the product to any specific structural or patentably distinct product. Furthermore, the Crowe-Science reference indicates that the protein is indeed functional and active (see page 707-708). In addition, the means by which the product does not distinguish the product from that of the prior art because the structure of the protein is still identical. Only in cases where the process by which the product is made forms a distinct structural product from that already taught, is the product patentable. Even in those cases, the product would by default constitute a structurally different product. Because the Office does not have the capacity to test whether there is at least 70% biologically active fusion protein in the composition taught by Crowe *et al*, and because the applicant has not set forth any substantive evidence to indicate that Crowe's composition is less than 70% biologically active, the claims are still anticipated by Crow *et al.*

New Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 8,10,11,26,37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a "composition", which is defined by Merrian-Webster Online as *"a product of mixing or combining various elements or ingredients"*. Currently, it is unclear as to what other element is comprised within the claimed composition.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 16 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising a receptor-Ig fusion protein. The specification teaches the construction of LT-beta-Ig and HVEM-Ig fusion proteins in vitro. However, the specification is devoid of teaching the use of a fusion construct in an in vivo setting. One of skill in the art would not be able to practice the invention, because the intended use of the product as a pharmaceutical composition has not been taught nor has there been any exemplification of its use in vivo. Furthermore, the specification has only provide the skilled artisan with guidance in terms of making the compositions comprising either LT-beta receptor-Ig or HVEM-Ig, and testing the fusion constructs for biologically activity. No guidance in terms of administering the composition in a subject has been taught or provided.

The use of a product in vitro can not be reasonably translated into in vivo usage without undue experimentation because it is well known that in vitro results are not predictable in vivo. The specification has only provided exemplification of biological activity in vitro and this cannot be correlated to in vivo activity. Thus, there is insufficient guidance and objective evidence that such teachings would be indicative of vivo

efficacy, i.e. in an individual; wherein it would not be predictable to one of skill in the art to use the product in vivo.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer

cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Claim Rejections - 35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 8,16,26,27, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth a composition comprising a fusion construct of LT-beta receptor-Ig

and or HVEM-Ig, and therefore the written description is not commensurate in scope to claims that read on any and all receptor-Ig fusion constructs, wherein the receptor is from the TNF family of receptors.

The claims recite a "receptor-Ig fusion proteins" as part of the invention. The written description for the "receptor-Ig fusion proteins", wherein the receptor is from the TNF family of receptors is provided on page 8 and 9, wherein it is disclosed that "TNF family of receptors" is any receptor which comprises "the canonical TNF family cysteine bridging patterns or any receptor which binds toi a defined member of the TNF family of receptors." However, the specification has not provided a written description for the broad genus of "receptor-Ig" fusion proteins, wherein the receptor portion is derived from the TNF family.

The specification has only provided support for two species within in this family, namely LT-beta receptor and HVEM, and such exemplification is not representative of the broad class of TNF family receptors claimed. Thus, it does not appear that the instant specification as-filed has adequate written description of the broad class of receptors claimed. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice a representative number of TNF family receptor-Ig fusion proteins. The genus of receptors claimed encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed. Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 102

10. Claims 8, 11,26-27,29, and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon *et al* (J. Biol. Chem. May 1997; 272(22):14272-14276). Kwon *et al* teach a composition comprising at least 70% biologically active receptor-Ig fusion protein, wherein the receptor is a member of the TNF family of receptors (see page 14273). More specifically, it is disclosed that the TR2 receptor is identical to HVEM (see page 14274). The specification defines "Ig fusion protein" as any fusion protein comprising the constant region of an immunoglobulin molecule (see page 8). Therefore, Kwon *et al* anticipates the claimed invention because they disclose a TR2-Fc fusion protein which is biologically active in inhibiting MLR-mediated PBL proliferation (see page 14275). Because the Office does not have the facilities to determine if less than 70% of the fusion protein is inactive, in the absence of evidence to the contrary, the composition taught by Kwon *et al* comprises at least 70% active receptor-Ig fusion protein. Furthermore, because the claims are drawn to the product *per se*, and if the product is known in the art, the means of making the product is considered an unpatentable distinction. Therefore, claims reciting culturing temperatures and conditions are also anticipated.

11. Claims 8,10,26-28, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Rennert *et al* (J. Exp. Med November 1996; 184:1999-2006). Rennert *et al* teach a composition comprising an LT-beta receptor-Ig fusion protein and TNF-R-Ig fusion protein (see page 1999 abstract). Both of these receptors are members of the TNF family of receptors (see page 1999), and showed biological activity (see page 1999 abstract – discusses the ability of the fusion proteinto disrupt development of the lymph

node). Further, because the Office does not have the facilities to determine that at least 70% of the protein was active, in the absence of evidence to the contrary, the compostion taught by Rennert *et al* comprised at least 70% biologically active fusion proteins. Furthermore, because the claims are drawn to the product *per se*, and if the product is known in the art, the means of making the product is considered an unpatentable distinction. Therefore, claims reciting culturing temperatures and conditions are also anticipated.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
April 19, 2004

GARY NICKOL
PRIMARY EXAMINER